

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference ARG/P33093	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/GB 03/03452	International filing date (day/month/year) 07.08.2003	Priority date (day/month/year) 09.08.2002
International Patent Classification (IPC) or both national classification and IPC C12P15/00		
Applicant GLAXO GROUP LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

I ☒ Basis of the opinion

II ☐ Priority

III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability



IV ☐ Lack of unity of invention

V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

VI ☐ Certain documents cited

VII ☐ Certain defects in the international application

VIII ☐ Certain observations on the international application

Date of submission of the demand 09.02.2004	Date of completion of this report 21.09.2004
Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Pinheiro Vieira, E Telephone No. +49 89 2399-7865 <div style="text-align: right;">  </div>

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB 03/03452

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-13 as originally filed

Claims, Numbers

1-33 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
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**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	10,17-20,22,24-26,28
	No: Claims	1-9,11-16,21,23,27,29-33
Inventive step (IS)	Yes: Claims	
	No: Claims	1-33
Industrial applicability (IA)	Yes: Claims	1-33
	No: Claims	

2. Citations and explanations

see separate sheet

V. Reasoned statement.

V.1 Cited documents.

1.1 Reference is made to the following documents:

- D1: PALMA N ET AL: PROCEEDINGS OF EUROPEAN CONGRESS BIOTECHNOLOGY, vol. 1, 1984, pages 533-542
- D2: KAVANAGH, FREDERICK ET AL.: vol. 37, 1951, pages 570-574
- D3: WO 99/21855 A (SMITHKLINE BEECHAM) 6 May 1999
- D4: WO 01/74788 A (SMITHKLINE BEECHAM PLC (GB)) 11 October 2001
- D5: US-A-4 247 542 (MICHEL KARL H ET AL) 27 January 1981
- D6: CH 650 531 A (RICHTER GEDEON VEGYESZET) 31 July 1985

1.2 D1 (summary; tables 1-3; figure 1) discloses pleuromutilin related metabolites isolated from cultures of various species of *Clitopilus* (e.g. *C. passeckerianus* and *C. pinsitus*, and *Psathyrella* and *Octojuga* species) with a water immiscible organic solvent, e.g. at about 10°C-50°C in a pH range of about 6-8, and crystallizing the obtained pleuromutilins.

D2 (abstract; page 571) discloses a process for preparing pleuromutilin by culturing pleuromutilins-producing organisms (e.g. from the species *Pleurotus Passeckerianus*), extracting the pleuromutilins with a water immiscible organic solvent, decolourisation using activated carbon (Norit A), crystallizing and recrystallizing the obtained pleuromutilins.

Documents D3 and D4 disclose pleuromutilin compounds falling with the scope of compounds with formulas (4A), (4B) and (5).

Document D5 (columns 5 and 7; examples) discloses the preparation of pleuromutilin derivatives isolated from *Octojuga pseudo pinsitus* NRRL11179, comprising extracting the pleuromutilins with a water immiscible organic solvent (e.g. toluene), the pH of the aqueous solution prior to extraction is in a range of about 6-8, crystallizing and recrystallizing the obtained pleuromutilins.

Document D6 concerns the extraction of an unfiltered fermentation broth with a water immiscible solvent with a pH of 7 to 9 (examples).

V.2 Novelty, inventive step and industrial applicability (Art. 33 PCT).

2.1 The present application concerns a method for the preparation of pleuromutilins by culturing pleuromutilins-producing organisms (e.g. from the species *Clitopilus*,

Octojuga, Gerronema, Psathyrella), extracting the pleuromutilins from the unfiltered culture medium with a water immiscible organic solvent (e.g. toluene or MIBK), e.g. at about 10°C-50°C, where the pH of the aqueous solution prior to extraction is in a range of about 6-8, and crystallizing the obtained pleuromutilins.

- 2.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-9, 11-16, 21, 23, 27, 29-33 is not new in the sense of Article 33(2) PCT.

D1 anticipates the subject matter of claims 1,2,4-8, 11-13, 29-33, D2 the subject matter of claims 1-4, 8, 12, 21, 23, 27 and 29-33 and D5 the subject matter of claims 1-2, 4-9, 11-16, 21, 23 and 27.

The Applicant should note that the term "mutant thereof" implies that other species (claim 5) or strains (claims 6 and 7) than the ones mentioned are encompassed by the claim and therefore, the species disclosed in the prior art, which perform the same function, are embraced by the claim (Art. 6 PCT).

The subject matter in claims 10, 17-20, 22, 24-26 and 28 is new as none of the documents D1, D2 or D5 discloses the water immiscible MIBK to extract and/or crystallize pleuromutilins (claims 10, 17 and 18), the crystallization of pleuromutilins from MIBK and a non-polar solvent-heptane- (claims 19 and 20), the removal of pleuromutilin 14-acetate selectively with ethyl acetate and heptane (claims 22 and 26) and the temperature ranges of claims 24, 25 and 28.

- 2.3 The features in claims 10, 17-20, 22, 24-26 and 28 appear to be merely conventional features in the art of fermentation, extraction and crystallization without bringing any apparent advantage to the known process of claim 1 (see documents D1, D2 and D5).

The Applicant is therefore, invited to show either by argumentation or technical evidence, that the claimed method on file possesses any advantage or/and surprising feature when compared with the methods of the prior art D1, D2 and D5 in order to enable the acknowledgement of the inventiveness of the application.

The Applicant is reminded that the ability to produce pleuromutilins metabolites is a wide spread property of the genus Clitopilus (see D1) and that the pleuromutilins claimed (claims 30-33) are known from D3 and D4.